REMARKS

Claims 1-48 are pending in this application. Claims 1-10 and 23-48 were previously withdrawn. Claims 11 and 18 are amended herein, and claim 17 is canceled. Upon entry of this amendment, claims 1-16 and 18-48 will be pending in this application.

Claims 11-22 were rejected in the Office Action. Each rejection is addressed individually below. The citations to the specification included throughout this amendment are to the paragraph numbers of the published application (US 2005/0136122).

I. Rejections Under 35 U.S.C. § 103(a)

The Office Action rejected all claims under 35 U.S.C. § 103(a) as obvious in light of various combinations of US 2002/0049281 ("Zhao"), European Patent Application 0416205 ("Prestwich"), Duranti *et al.*, Dermatologic Surgery 24:1317-1325 (1998) ("Duranti"), WO/9602209 ("Lawin"), and U.S. Patent No. 5,942,241 ("Chasin"). Applicants respectfully traverse this rejection.

The Supreme Court recently ruled that in an obviousness inquiry:

> [o]ften, it will be necessary ... to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an ***apparent reason to combine*** the known elements in the fashion claimed by the patent at issue. To facilitate this review, this ***analysis should be made explicit.***

KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1740-41 (2007) (emphasis added). The Supreme Court also stated that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Applicants maintain that the Office Action does not establish a *prima facie* case of obviousness under this standard.

A. Zhao and Prestwich

Claims 11, 13-14, 17, and 19 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhao in light of Prestwich.

As an initial matter, claim 17 has been canceled herein, rendering rejection of this claim moot.

Amended independent claim 11 recites:

> A method of augmenting tissue in a subject that is in need of tissue augmentation, the method comprising:
>
> a) inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with a crosslinked HA composition that includes crosslinked, water-insoluble, hydrated HA gel particles, wherein the HA includes crosslinks represented by the following structural formula:
>
> HA'—U—R_2—U—HA'
>
> wherein:
>
> each HA' is the same or different crosslinked HA' molecule;
>
> each U is independently an optionally substituted O-acyl isourea or N-acyl urea;
>
> and R_2 is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl,

wherein the HA gel particles have an average particle diameter distribution selected from the group consisting of a hydrated particle average diameter between about 20 μm and about 1000 μm, and a dehydrated particle average diameter between about 10 μm and about 500 μm; and

b) applying force to the syringe, whereby at least a portion of the HA composition is delivered into the subject.

Claims 13-14, and 19 depend directly or indirectly from claim 11 and add various limitations including the addition of bioactive agents (*e.g.*, lidocaine) to the composition.

The Office Action asserts that Zhao teaches "that cross-linked HA derivatives may be used in a variety of forms including beads ... , and are useful in hard and soft tissue augmentation ... , and for delivery of therapeutically active agents such as anti-inflammatory agents, antibiotics, analgesics, and wound healing promoters ..." (Office Action at page 4, last paragraph, citations omitted). Applicants respectfully disagree with this characterization of Zhao.

Zhao discloses hyaluronic acid ("HA") compositions wherein the HA is crosslinked to polymers other than HA via two or more different functional bonds (*see*, *e.g.*, Zhao at ¶¶ 15-19). Zhao teaches that crosslinking HA to different polymers results in "improved biostability of HA based on the degree of crosslinking and selection of the second polymer" (Zhao at ¶ 15). Zhao also teaches that "the properties of the second (or subsequent) polymer will to some extent influence the properties of the final cross-linked product. The second or subsequent polymer should therefore be selected having regard to the properties desired in the final product, and should be compatible with and even enhance these properties" (Zhao at ¶ 20). Therefore, Zhao teaches that the second polymer will enhance the properties of the overall HA/polymer combination, and that HA crosslinked to a polymer other than HA is superior to HA crosslinked only to HA. Thus Zhao teaches away from the use of HA alone. Furthermore, Zhao does not teach HA particles made only of crosslinked HA. Additionally, Zhao does not teach a specific particle size for the compositions described therein.

Furthermore, Zhao distinguishes its disclosure from the prior art by stating "[n]one of the aforementioned documents describe products in which HA is linked to one or more polymer molecules (which may be the same or different) by means of two different types of cross-linking bonds" (Zhao at ¶ 14). Zhao refers to this as "double crosslinked" HA (Zhao ¶ 19). Zhao teaches that "double crosslinked" HA is superior to "single crosslinked" HA because "double crosslinked" HA has a higher degree of crosslinking, which imparts greater stability (Zhao ¶ 76). Thus Zhao teaches away from the use of "single crosslinked" HA.

Applicants' claimed HA particles contain only crosslinked HA. No other polymers are crosslinked to the HA in Applicants' claimed HA particles. Applicants' claimed HA particles are "single crosslinked" HA, as defined by Zhao ¶ 19, because they are crosslinked by only one type of functional bond. Therefore, Applicants' claimed HA particles are distinct from the HA/polymer crosslinked compositions of Zhao. Furthermore, Applicants' claimed HA particles possess desired properties (*e.g.*, extrusion force, viscosity, biostability) despite the lack of a second polymer. Zhao teaches away from being able to obtain desired properties using HA that is not crosslinked to a different polymer via "double crosslinks." Therefore, one of skill in the art would not have a reasonable likelihood of success in adapting the teachings of Zhao to form Applicants' claimed HA particles. Additionally, Applicants' claimed HA particles have a hydrated particle average diameter between about 20 μm and about 1000 μm, or a dehydrated particle average diameter between about 10 μm and about 500 μm. Zhao does not teach specific particle sizes.

Prestwich does not address or cure the deficiencies in Zhao. Prestwich teaches N-acylurea and O-acylisourea derivatives of HA (Prestwich at page 3, line 40). Prestwich does not teach HA particles, let alone HA particles for tissue augmentation or ranges for HA particle diameter. Prestwich also does not teach how to obtain Applicants' desired properties such as extrusion force. Because Zhao teaches away from the use of HA that is not crosslinked to another polymer via "double crosslinks," one of skill in the art would not be motivated to use the "single crosslinked" HA of Prestwich to form HA particles that are not crosslinked to another polymer in a method for tissue augmentation. Instead, one of skill in the art would, based on Zhao, crosslink HA to a second polymer using "double crosslinks." Furthermore, neither Prestwich nor Zhao alone or in

combination teach any HA particle sizes, let alone HA particle sizes for use in a method of tissue augmentation.

Accordingly, Applicants respectfully submit that this 35 U.S.C. § 103(a) rejection of claims 11, 13-14, and 19 has been overcome, and request that it be withdrawn.

B. Zhao, Duranti, and Lawin

Claims 11-14, 17, and 19-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhao in light of Duranti and Lawin.

As an initial matter, claim 17 has been canceled herein, rendering rejection of this claim moot.

Amended independent claim 11 is recited above. Claims 12-14 and 19-22 depend directly or indirectly from claim 11 and add various limitations including storage modulus, kinematic viscosity, and the addition of bioactive agents (*e.g.*, lidocaine) to the composition.

As detailed above, Zhao discloses hyaluronic acid ("HA") compositions wherein the HA is crosslinked with polymers other than HA via two or more different functional bonds (*see*, *e.g.*, Zhao at ¶¶ 15-19). Zhao does not disclose crosslinked HA particles containing only crosslinked HA in a method for tissue augmentation. Furthermore, Zhao does not recite ranges for particle diameter, storage modulus, or kinematic viscosity for any of the compositions disclosed therein, let alone for HA particles containing only crosslinked HA. Therefore, Zhao does not disclose the subject matter of Applicants' instant claims.

Duranti does not cure or address the deficiencies in Zhao. Duranti discloses HA gel that is "chemically stabilized through permanent ***epoxidic*** cross-links that the manufacturer reports to alter only about 1% of the hyaluronan molecular network" (Duranti at page 1318, col. 1, last paragraph) (emphasis added). Duranti does not disclose HA particles crosslinked via ***O-acyl isourea or N-acyl urea*** as recited in the present claims. Thus Duranti teaches the use of a different material than that claimed by Applicants. Furthermore, Duranti does not disclose Applicants' limitations regarding

particle diameter, storage modulus, kinematic viscosity, and the addition of bioactive agents. Additionally, one of skill in the art would not combine the teachings of Duranti with the teachings of Zhao. Duranti states that "[t]he implantation syringe contains only hyaluronic acid gel and water" (Duranti at page 1318, first paragraph), thus Duranti does not teach the use of another polymer with HA. Because Zhao teaches away from the use of HA that is not crosslinked to another polymer, one of skill in the art would not be motivated to use the HA of Duranti to form HA particles that are not crosslinked to another polymer in a method for tissue augmentation.

Lawin does not address or cure the deficiencies in Zhao and Duranti. Lawin teaches the use of ***carbon or metallic*** microbeads in a carrier solution (Lawin at page 2, second full paragraph; page 3, first paragraph), ***not*** crosslinked ***HA particles***. Lawin's carbon or metallic microbeads are used to treat urinary incontinence and vesicourethral reflux (Lawin at page 1, last paragraph), or to reposition organs such as the lungs, liver, spleen, brain, kidney, and lymph nodes (Lawin at page 2, first paragraph). Although Lawin states that HA may be used as a ***carrier*** for the carbon or metallic microbeads, the ***microbeads themselves*** do not contain any HA. Therefore, Lawin does not disclose crosslinked HA particles for tissue augmentation. Thus one of skill in the art would not combine the teachings of Lawin with those of Zhao and Duranti, as these references are drawn to the use of different materials for different applications. And none of these materials are the same as those recited in Applicants' claims, namely crosslinked HA particles for use in a method for tissue augmentation.

Accordingly, Applicants respectfully submit that this 35 U.S.C. § 103(a) rejection of claims 11-14 and 19-22 has been overcome and that the rejection be withdrawn.

C. Zhao and Chasin

Claims 11, 13-19, and 20-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhao in light of Chasin.

As an initial matter, claim 17 has been canceled herein, rendering rejection of this claim moot.

Independent claim 11 is recited above. Claims 13-16, 18-19, and 20-22 depend directly or indirectly from claim 11 and add various limitations, including particle diameter distribution, storage modulus, kinematic viscosity, and the addition of bioactive agents (*e.g.*, lidocaine) to the composition.

Zhao is summarized above. Zhao discloses hyaluronic acid ("HA") compositions wherein the HA is crosslinked with polymers other than HA via two or more different functional bonds (*see, e.g.*, Zhao at ¶¶ 15-19). Zhao does not disclose crosslinked HA particles made only of crosslinked HA in a method for tissue augmentation. Furthermore, Zhao does not recite ranges for particle diameter, particle diameter distribution, storage modulus, or kinematic viscosity for any of the compositions disclosed therein, let alone for HA particles containing only crosslinked HA. Therefore, Zhao does not disclose the subject matter of Applicants' instant claims.

Chasin does not address or cure the deficiencies in Zhao. Chasin teaches "pharmaceutically acceptable augmenting agent or agents in conjunction with a local anesthetic in controlled release form that significantly increases the time period of local anesthesia when administered at a site in a patient" (Chasin at col. 5, lines 31-27). The "augmenting agents" used in Chasin's invention "are compositions or compounds that prolong the duration of local anesthesia and/or enhance the effectiveness of local anesthetic agents when delivered to the site of local anesthetic administration before, simultaneously with or after the local anesthetic is administered" (Chasin at col. 6, lines 59-64). Chasin does not disclose the use of crosslinked HA particles in a method for tissue augmentation, nor does Chasin recite ranges for the particle diameter, particle diameter distribution, storage modulus, or kinematic viscosity for such particles.

Although Chasin states that HA may be used as a carrier for the anesthetic and augmenting agent, Chasin also states that "[a]ny pharmaceutically acceptable carrier vehicle or formulation suitable for local implantation, infiltration or injection in proximity to a nerve that is able to provide a controlled release of a local anesthetic agent and/or augmenting agent may be employed to provide for prolonged local anesthesia as needed" (Chasin as col. 11, lines 32-37). Furthermore, Chasin provides a long list of carriers suitable for use with the invention disclosed therein (*see*

Chasin, col. 12, line 27 to col. 14, line 7) without providing any suggestion or motivation to select HA from this list. Chasin certainly provides no motivation or suggestion to create HA microbeads instead of carbon or metallic microbeads and to use HA microbeads in a method of tissue augmentation.

Zhao and Chasin, either alone or in combination, do not teach or suggest the use of crosslinked HA particles in a method of tissue augmentation. Accordingly, Applicants respectfully submit that this 35 U.S.C. § 103(a) rejection of claims 11, 13-16, 18-19, and 20-22 has been overcome and that the rejection be withdrawn.

II. Rejection Made Without Reference to 35 U.S.C. § 103(a)

Claims 17, 18, and 20-22 were rejected without citation to 35 U.S.C. § 103(a) or to any references. The Office Action Asserts that these claims "are drawn to physical properties of the HA formulation. One of ordinary skill in the art would expect that the claimed formulation would behave wherein the distribution is a multimodal distribution and possess a storage modulus G' of at least 400 Pa and a kinematic viscosity of at least 100 Pa" (Office Action at page 10, first full paragraph). Applicants respectfully traverse this rejection.

As an initial matter, claim 17 has been canceled herein, rendering rejection of this claim moot.

Furthermore, the Office Action does not cite any section of 35 U.S.C. as the basis of this rejection. Applicants assume that this is an obviousness rejection under 35 U.S.C. § 103(a). Furthermore, the Office Action does not cite any references in support of this assertion. Therefore, the analysis underlying this rejection has not been made explicit as required under *KSR*. Thus the Office Action fails to establish a *prima facie* case of obviousness with this rejection.

Accordingly, Applicants respectfully request that this 35 U.S.C. § 103(a) rejection be reconsidered and withdrawn.

III. Conclusion

In view of the above arguments, Applicants submit that the rejections in the Office Action of June 10, 2008 have been overcome and the pending claims are in condition for allowance.

Applicants believe no fee is due with this response. However, please charge any payments du or credit any overpayments to our Deposit Account No. 08-0219, under Order No. 0103343.00128US1 from which the undersigned is authorized to draw.

Respectfully submitted,

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